

ORIGINAL RESEARCH ARTICLE

Drugs R D 2011; 11 (2): 171–190
1179-6901/11/0002-0171

© 2011 Mori et al., publisher and licensee Adis Data Information BV. This is an open access article published under the terms of the Creative Commons License "Attribution-NonCommercial-NoDerivative 3.0" (<http://creativecommons.org/licenses/by-nc-nd/3.0/>) which permits non-commercial use, distribution, and reproduction, provided the original work is properly cited and not altered.

Artist[®] Tablets (Carvedilol) for Hypertensive Patients in Japan

Results of a Drug Use Survey

Yoshihiro Mori,¹ Yasuhiro Nishikawa,² Tomoko Iizuka,¹ Natsuko Zenimura,¹ Takuyuki Matsumoto,¹ Katsutoshi Hiramatsu¹ and Masahiro Komiya¹

1 Post Marketing Study Management Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

2 R&D Planning Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

Abstract

Background: In Japan, when pharmaceutical companies launch a new drug, they are obligated to conduct a post-marketing survey to evaluate the safety and efficacy of the drug in accordance with Good Post-Marketing Surveillance Practice under Article 14.4 (re-examination) of the Pharmaceutical Affairs Law at contracted medical institutions. We report the results of a drug use survey, which we conducted as a post-marketing survey.

Objective: This prospective post-marketing drug use survey was conducted to assess the safety and efficacy of the β -adrenergic receptor antagonist (β -blocker) Artist[®] Tablets (carvedilol) in patients with hypertension in Japan.

Patients: Patients were carvedilol-naïve and had essential hypertension or renal parenchymal hypertension.

Methods: This was a prospective survey conducted over 3 years from October 1993 to September 1996. The standard observation period for the patients was defined as 12 weeks of treatment with carvedilol.

Results: We collected data on 4961 patients at 561 medical institutions who had not been previously treated with carvedilol; 4574 patients were included in the safety analysis and 4422 in the efficacy analysis. The incidence of adverse drug reactions (the proportion of patients with adverse drug reactions) was 4.31% (197 of 4574 patients), which is less than that shown in the pre-approval clinical trial of carvedilol (6.85% [68 of 993]). The most common adverse drug reactions were bradycardia, dizziness, hypotension, headache, and feeling light-headed.

After 12 weeks' treatment with carvedilol, systolic/diastolic blood pressure (SBP/DBP) was reduced from $168.2 \pm 18.6/95.7 \pm 11.3$ mmHg at baseline to $144.3 \pm 17.3/83.4 \pm 10.8$ mmHg. Patients were classified according to which anti-hypertensive drug they had been using when carvedilol treatment was initiated. Co-administered agents were calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), diuretics, and α -adrenergic receptor antagonists (α -blockers). At 12 weeks, the change in SBP/DBP in the monotherapy group was $-22.7/-12.2$ mmHg and that of each combination therapy

subgroup, CCB, ACEI, diuretic, and β -blocker, was $-26.1/-12.7$ mmHg, $-25.4/-11.9$ mmHg, $-26.3/-13.0$ mmHg, and $-24.4/-11.5$ mmHg, respectively. The achievement rates for target BP ($<140/90$ mmHg) were 29.5% in the monotherapy group, 34.8% in the CCB group, 31.3% in the ACEI group, 31.8% in the diuretic group, and 32.4% in the β -blocker group. There was no significant difference in the achievement of target BP among the four combination therapy subgroups ($p=0.475$). These results indicate that carvedilol exerts reasonable BP reduction regardless of whether it is used as monotherapy or in combination therapy, and that the effect is not influenced by the coadministered drug. Moreover, carvedilol was also effective in reducing BP levels in elderly patients (≥ 65 years) and in patients with diabetes mellitus or renal diseases.

Conclusions: The results of this study reflect the results of clinical trials up to the time of approval and it was confirmed that carvedilol is a highly useful drug in the treatment of hypertension.

Introduction

For the management of hypertension, risk stratification should be based on the presence or absence of risk factors other than blood pressure (BP), such as hypertensive organ damage or cardiovascular disease. If needed, an antihypertensive drug may be initiated to achieve BP goal. If hypertension is complicated with risk factors, such as diabetes mellitus, target organ damage, or renal dysfunction, aggressive management of hypertension is important to attain target BP goals as defined in the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004).^[1] However, it is difficult to achieve target BP goals with a single antihypertensive drug and often combined administration of two or more drugs is required.

Currently available antihypertensive drugs in Japan include calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), diuretics, β -adrenergic receptor antagonists (β -blockers), and α -adrenergic receptor antagonists (α -blockers). Most antihypertensive drugs have been demonstrated to have not only an antihypertensive effect, but also cerebrovascular/cardiovascular protective effects. Based on results of large-scale clinical studies, several guidelines^[1-4] recommend that depending on their pharmacologic properties, some

classes of antihypertensive drugs should be aggressively used and some should be contraindicated in patients with compelling indications such as established cardiovascular disease, diabetes, chronic kidney disease, or recurrent stroke. Regarding combined administration of two or more drugs, in order to select the best antihypertensive drugs for each patient, guidelines^[1-4] recommend suitable combinations based on best evidence. These combinations are expected to provide additive or synergistic effects; however, the recommendations differ between the various guidelines.

β -Blockers are aggressively indicated for the treatment of hypertension associated with angina pectoris, myocardial infarction, tachycardia, and/or heart failure, and are recommended for the prevention of recurrence of myocardial infarction or occurrence of ischemic heart disease, and to improve prognosis in patients with heart failure. For cardioprotection and strict control of BP in patients with these risks, the use of β -blockers is of great significance. However, the blockade of β -receptors can induce adverse effects such as increased peripheral vascular resistance, decreased local circulation, excessive impairment of cardiac function, coronary vasospasm, and bronchoconstriction. However, most β -blockers are less likely to be used than antihypertensive drugs that are associated with a lower incidence of adverse drug reactions (ADRs), such as CCBs,

ACEIs, and ARBs, because of concern of adverse effects on glucose/lipid metabolism.

Carvedilol, with an improved ADR profile, was synthesized by Boehringer-Mannheim (currently, Hoffmann-La Roche, Basel, Switzerland), and clinically developed and launched in Japan by Daiichi Pharmaceutical Co., Ltd. (currently, Daiichi Sankyo Co., Ltd., Tokyo, Japan) as a cardiac nonselective β -blocking agent with peripheral vasodilatation (mainly based on α_1 -blocking action).^[5] Clinical studies have demonstrated that carvedilol has a long-lasting antihypertensive effect that allows once-daily administration without adversely affecting glucose/lipid metabolism, and has favorable efficacy when used alone or in combination with other drugs.^[6-14] Carvedilol is the only β -blocker indicated for the treatment of chronic heart failure in Japan. Based on accumulated evidence in the treatment of chronic heart failure,^[15-19] carvedilol has received a certain level of positive evaluation in Japan and other countries.^[20,21] However, there have been no reports on the antihypertensive efficacy or safety of carvedilol when being used in many hypertensive patients in daily clinical practice in Japan. In particular, no large-scale study had been conducted to investigate whether β -blockers could aggravate glucose metabolism, or not, in Japanese patients with diabetes. In addition, it is known that elderly individuals generally respond less well to β -blockers because of their lower renin activity.

This prospective survey, conducted between October 1993 and September 1996, sought to assess the use of carvedilol in patients with hypertension in Japan. This report will also address the efficacy and safety of carvedilol alone and in combination with other drugs, in elderly patients and in high-risk patients with diabetes or renal disease, conditions that are more likely to be found in elderly individuals.

Patients and Methods

Patients

This survey was conducted in accordance with Good Post-Marketing Surveillance Practice^[22]

under Article 14.4 (re-examination) of the Pharmaceutical Affairs Law at contracted medical institutions. Patients were carvedilol-naïve and had essential hypertension or renal parenchymal hypertension. After a contract was concluded at the medical institution, patients with these diseases who had not been previously treated with carvedilol and who received carvedilol during the observation period were investigated consecutively.

Dosage and Administration

Carvedilol was administered at the discretion of physicians participating in the survey, and was prescribed according to the dosage and administration in the package insert; the usual adult dosage for oral use is carvedilol 10–20 mg once daily. The dosage could be adjusted according to each patient's age and symptoms. Neither prior treatment nor combination drugs were restricted. The standard observation period was 12 weeks, during which time patients were treated with carvedilol. If patients dropped out or withdrew from the survey, they were followed-up until that time.

Assessments

Patient Demographics

Data collected included patient initials, medical record number, date of birth, sex (pregnancy status for women), in- or outpatient status, diagnosis (target disease), severity (the WHO classification), duration of disease, presence/absence of complications, previous medical history, history of allergy, family history of hypertension, previous use of antihypertensive medications before the initiation of carvedilol, and concomitant use of other antihypertensive medications.

Carvedilol Dosage and Administration

The duration of carvedilol treatment and daily dose were recorded.

Clinical Observations

Data on systolic blood pressure (SBP)/diastolic blood pressure (DBP) and pulse rate were collected.

Laboratory Analyses

The laboratory analyses included hematology, blood chemistry, and urinalysis.

Adverse Drug Reactions

The name, severity, progress, medication taken for an ADR, outcome, drug-event relationship, and suspected concomitant medication were recorded for all ADRs.

Diseases that Developed During the Course of Carvedilol Treatment

The name and progression of diseases that developed during the course of carvedilol treatment were recorded.

Data Handling and Collection/Analytical Procedures

The safety population comprised patients who completed a case report form. Excluded were those who (i) received carvedilol during periods other than the survey period; (ii) started the drug before a contract was concluded; (iii) provided two case report forms; (iv) did not revisit the medical institutions after the initial visit; and (v) were not evaluated for ADRs.

The efficacy population comprised patients from the safety population and excluded patients (i) with unknown target disease or who used carvedilol for the treatment of a condition other than the target disease; and (ii) who were not evaluated or could not be evaluated for efficacy.

Assessment of efficacy was performed by each physician. The antihypertensive effect of carvedilol was assessed according to the following four criteria: 'decreased', 'tended to be decreased', 'unchanged', and 'increased'.

The demographic data of the patients and the incidence of ADRs (the proportion of the patients with ADRs) in the safety population were analyzed using Fisher's direct probability method. Changes from baseline in SBP/DBP and pulse rate were analyzed at week 12 using paired t-test and at weeks 2, 4, 6, 8, 10, and 12 according to Dunnett's multiple comparison test. In the physicians' assessment of efficacy, a 95% confidence interval was calculated for decrease in BP. All statistical tests were performed

using a two-sided 5% significance level. The figures are presented as mean \pm standard deviation (SD).

The observed ADRs were classified using preferred terms by each System Organ Class according to the 1996 version of the Japanese Adverse Drug Reaction Terminology.

Results

Patient Number and Disposition

Case report forms were collected from 4961 patients at 561 medical institutions throughout Japan. Among the total 4961 patients, 81 received carvedilol during periods other than the survey period, 162 had started the drug before a contract was concluded, 56 provided two case report forms, 85 did not revisit the medical institute after the initial visit, and three were not evaluated for ADRs; these 387 patients were excluded from the safety analyses. The remaining 4574 patients were included in the safety population. Among the safety population, five had unknown target disease or used carvedilol for a condition other than the target disease (renovascular hypertension), and 147 were not evaluated or could not be evaluated for efficacy; these 152 patients were excluded from the efficacy analyses. The remaining 4422 patients were included in the efficacy population. Patient disposition is shown in figure 1.

Patient Demographics

The demographic characteristics of patients comprising the safety population are presented in table I. The safety population had nearly equal numbers of males and females. Elderly patients aged ≥ 65 years accounted for 38.4% (1757 patients), including 579 advanced elderly patients aged ≥ 75 years (12.7%). The majority of the safety population were patients with essential hypertension (97.7%; $n = 4468$), and those with renal parenchymal hypertension accounted for 2.2% (101 patients). The severity of hypertension was graded as follows: 2713 patients (59.3%) had WHO grade I, 1037 (22.7%) grade II, and 586 (12.8%) grade III. Heart failure was found as a co-existing condition of hypertension in the largest number of the safety population (853 patients

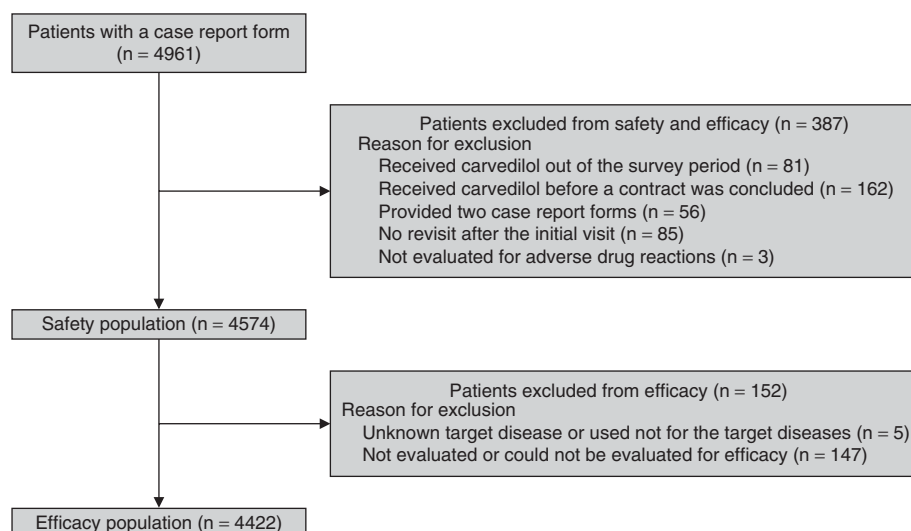


Fig. 1. Patient disposition.

[18.7%]], followed by hepatic disease (536 patients [11.7%]), diabetes (500 patients [10.9%]), and renal disease (289 patients [6.3%]). During the survey, 2039 patients (44.6%) initiated carvedilol treatment at a dose of 10 mg/day and 2509 patients (54.9%) with 20 mg/day. During the carvedilol treatment period, a total of 2293 patients (50.1%) concomitantly used other antihypertensive medications; CCBs were the most commonly used by 1698 patients (37.1%).

Safety

Adverse Drug Reactions

Table II provides a list of patient-reported ADRs. Among the 4574 patients who comprised the safety population, the overall incidence of ADRs was 4.31% (197 of 4574), which was lower than the reported 6.85% (68 of 993 patients with essential hypertension or renal parenchymal hypertension) for the approval of carvedilol. The most common ADR (preferred terms) was bradycardia (24 events, 0.52%), followed by dizziness (19 events, 0.42%), hypotension (15 events, 0.33%), and headache and light-headed feeling (nine events each, 0.20%). Four patients had five ADRs that were judged to be serious by their physicians – one event each of consciousness loss, cardiac failure, blood pres-

sure decreased, status asthmaticus, and erection decreased (all are preferred terms).

Adverse Drug Reactions by Demographic Factors

Table III presents ADRs stratified by selected demographic factors. A significant difference in the incidence rate of ADRs between strata was found for age, severity (WHO classification), presence/absence of complications (renal disease), previous use of antihypertensive medications before the initiation of carvedilol, total number of days of carvedilol treatment, and concomitant use of other antihypertensive medications, as summarized here.

Age

The incidence rate in elderly patients (≥ 65 years) was 5.18% (91 of 1757 patients), which was significantly higher than 3.76% in non-elderly patients (106 of 2816 patients; $p=0.025$). This subgroup had a significantly higher incidence of 'general cardiovascular disorders' ($p<0.001$) and reported four or more events of the following ADRs (preferred terms): bradycardia (14 events), hypotension (12 events), dizziness (ten events), light-headed feeling (five events), weakness (four events), headache (four events), and cardiothoracic ratio increased (four events).

Table I. Demographic characteristics of the 4574 patients in the safety population

Demographic factor/stratum	No. of patients (%) ^a
Gender	
Male	2203 (48.2)
Female	2369 (51.8)
pregnancy status: no	2368 (100)
yes	1 (0)
Not stated	2 (0)
Age (years)	
Mean±SD (range)	60.8±11.7 (16–99)
<15	0 (0.0)
15 to <65	2816 (61.6)
≥65	1757 (38.4)
65 to <75	1178 (25.8)
≥75	579 (12.7)
Unknown/not stated	1
Diagnosis (target disease)	
Essential hypertension	4468 (97.7)
Renal parenchymal hypertension	101 (2.2)
Renovascular hypertension	1 (0.0)
Unknown	4 (0.1)
In-/outpatient status	
Inpatient	173 (3.8)
Outpatient	4177 (91.3)
In- ↔ outpatient	173 (3.8)
Unknown/not stated	51 (1.1)
Severity (WHO classification)	
Grade I	2713 (59.3)
Grade II	1037 (22.7)
Grade III	586 (12.8)
Unknown/not stated	238 (5.2)
Complications (including overlapping)	
No	1876 (41.0)
Yes	2591 (56.7)
hepatic disease	536 (11.7)
renal disease	289 (6.3)
heart disease	853 (18.7)
diabetes mellitus	500 (10.9)
unknown/not stated	107 (2.3)
Creatinine at baseline (mg/dL)	
<1.0	1316 (28.8)
1.0 to <3.0	720 (15.7)
3.0 to <6.0	14 (0.3)
≥6.0	31 (0.7)
Unknown/not stated	2493 (54.5)

*Continued***Table I.** Contd

Demographic factor/stratum	No. of patients (%) ^a
Previous antihypertensive medications (including overlapping)	
No	1822 (39.8)
Yes	2471 (54.0)
calcium channel blockers	1559 (34.1)
angiotensin-converting enzyme inhibitors	873 (19.1)
diuretics	148 (3.2)
β-blockers	548 (12.0)
α-blockers	210 (4.6)
others	56 (1.2)
Unknown/not stated	281 (6.1)
Initial daily dose (mg)	
<10	7 (0.2)
10	2039 (44.6)
20	2509 (54.9)
≥21	18 (0.4)
Unknown/not stated	1 (0.0)
Duration of carvedilol treatment (mo)	
<1	254 (5.6)
≥1	4316 (94.4)
Unknown/not stated	4 (0.1)
Concomitant medications (including overlapping)	
No	1124 (24.6)
Yes	3322 (72.6)
other antihypertensive medications	2293 (50.1)
calcium channel blockers ^b	1698 (37.1)
angiotensin-converting enzyme inhibitors ^b	785 (17.2)
diuretics ^b	201 (4.4)
β-blockers	58 (1.3)
α-blockers	148 (3.2)
others	58 (1.3)
hypoglycemic drugs	265 (5.8)
Unknown/not stated	128 (2.8)

a Unless stated otherwise.

b Includes medications that the patient received for conditions other than hypertension.

α-blockers = α-adrenergic receptor antagonists; β-blockers = β-adrenergic receptor antagonists; In- ↔ outpatient = patients who were constantly in and out of hospital.

Severity (WHO Classification)

When stratified by severity (WHO classification), the incidence rate was 3.83% (104 of 2713 patients) for grade I, 3.95% (41 of 1037 patients) for grade II, and 7.68% (45 of 586 patients) for grade III, with a significantly higher incidence rate for grade III ($p < 0.001$). Patients with grade III had

significantly more 'body as a whole, general disorders' and 'general cardiovascular disorders' ($p=0.010$ and $p=0.004$, respectively). In this subgroup, three or more events of the following ADRs (preferred terms) were reported: bradycardia (six events), hypotension (five events), dizziness (five events), light-headed feeling (three events), queasy (three events), and cardiothoracic ratio increased (three events).

Complications (Renal Disease)

For patients with complications, the incidence of ADRs was significantly higher than in those without complications (5.29% [137 of 2591] vs 2.88% [54 of 1876]; $p<0.001$). When ADRs were stratified by the presence/absence of renal disease complications, a significant difference was seen between patients with renal disease complications (7.61% [22 of 289]) and those without (4.10% [174 of 4244]) [$p=0.010$], although no significant difference was observed when stratified by the presence/absence of hepatic disease, cardiac disease, or diabetes. Patients with renal disease complications had significantly higher incidence rates of ADRs – body as a whole, general disorders, central and peripheral nervous system disorders, general cardiovascular disorders, and respiratory system disorders ($p=0.026$, $p=0.041$, $p=0.006$, and $p=0.024$, respectively). In this subgroup, ADRs (preferred terms) that occurred at two events or more were light-headed feeling (three events), headache dull (two events), dizziness (two events), hypotension (two events), and cardiothoracic ratio increased (two events).

Previous Use of Antihypertensive Medications

The incidence of ADRs in patients who had used antihypertensive medications before the initiation of carvedilol was 5.38% (133 of 2471 patients), which was significantly higher than the 3.07% (56 of 1822 patients) in patients who had not previously used any antihypertensive medications ($p<0.001$). Central and peripheral nervous system disorders and gastrointestinal system disorders were reported significantly more often by patients who had used antihypertensive medications ($p=0.013$ and $p=0.049$, respectively). There was no significant difference in the incidence rate of general cardiovascular disorders ($p=0.241$). Five or more

events of the following ADRs (preferred terms) were reported in this subgroup: bradycardia (15 events), dizziness (14 events), hypotension (11 events), headache (eight events), queasy (seven events), headache dull (five events), and light-headed feeling (five events).

Total Number of Days of Carvedilol Treatment

The incidence rate of ADRs in the stratum of '<1 month' for total number of days of carvedilol treatment was 32.68% (83 of 254 patients), significantly higher than 2.64% (114 of 4316 patients) in the stratum of '≥1 month' ($p<0.001$). There were significantly more body as a whole, general disorders ($p<0.001$); skin and appendages disorders ($p=0.011$); central and peripheral nervous system disorders ($p<0.001$); psychiatric disorders ($p=0.017$); gastrointestinal system disorders ($p<0.001$); general cardiovascular disorders ($p<0.001$); heart rate and rhythm disorders ($p<0.001$); and respiratory system disorders ($p<0.001$) in the stratum of '<1 month'. ADRs (preferred terms) that were observed at five or more events in this stratum were dizziness (ten events), hypotension (ten events), bradycardia (nine events), queasy (six events), and light-headed feeling (five events).

Concomitant Use of Other Antihypertensive Medications

For patients that concomitantly used other antihypertensive medications, the incidence of ADRs was 4.93% (113 of 2293 patients), significantly higher than that reported in the cohort that did not concomitantly use other antihypertensive agents (3.68% [84 of 2280 patients]) [$p=0.041$]. The incidence of heart rate and rhythm disorders was significantly higher in patients with concomitant use ($p=0.019$), who reported five or more events of the following ADRs: bradycardia (13 events), dizziness (12 events), hypotension (11 events), queasy (six events), light-headed feeling (five events), and GPT increased (five events) [all are preferred terms].

Changes in Laboratory Parameters

Table IV shows the mean changes from baseline in hematologic and blood chemical parameters in patients who underwent laboratory tests before and after the initiation of carvedilol treatment.

Table II. Adverse drug reactions (ADRs) reported in the safety population^a

System Organ Class and preferred term	Number of ADRs (incidence rate [%])
Skin and appendages disorders	9 (0.20)
Eczema	1 (0.02)
Eczema acute	1 (0.02)
Itching	3 (0.07)
Eruption lichenoid	1 (0.02)
Rash	2 (0.04)
Eruption	1 (0.02)
Drug eruption	1 (0.02)
Xanthomatosis	1 (0.02)
Central and peripheral nervous system disorders	52 (1.14)
Inarticulateness	1 (0.02)
Twilight state	1 (0.02)
Headache	9 (0.20)
Headache dull	7 (0.15)
Head discomfort	1 (0.02)
Numbness of fingers	3 (0.07)
Dizziness	19 (0.42)
Dizziness on standing up	3 (0.07)
Light-headed feeling	9 (0.20)
Wooziness	1 (0.02)
Autonomic nervous system disorders	2 (0.04)
Oral dryness	1 (0.02)
Consciousness loss	1 (0.02)
Vision disorders	2 (0.04)
Eye prick, pain of	1 (0.02)
Vision blurred	1 (0.02)
Psychiatric disorders	4 (0.09)
Sleepiness	1 (0.02)
Anxiety	1 (0.02)
Depressed state	1 (0.02)
Feeling floating	1 (0.02)
Gastrointestinal system disorders	28 (0.61)
Gastritis	1 (0.02)
Queasy	7 (0.15)
Nausea	3 (0.07)
Retching	1 (0.02)
Vomiting	1 (0.02)
Diarrhea	2 (0.04)
Hiccup	1 (0.02)
Stomach feeling heavy	1 (0.02)
Heartburn	1 (0.02)

*Continued***Table II.** Contd

System Organ Class and preferred term	Number of ADRs (incidence rate [%])
Anorexia	2 (0.04)
Appetite decreased	1 (0.02)
Stomach pressure, sensation of	1 (0.02)
Stomach discomfort	4 (0.09)
Abdominal pain	2 (0.04)
Abdominal discomfort	1 (0.02)
Constipation	2 (0.04)
Abdominal enlarged, feeling of	1 (0.02)
Liver and biliary system disorders	7 (0.15)
GOT increased	6 (0.13)
GPT increased	7 (0.15)
Metabolic and nutritional disorders	15 (0.33)
ALP increased	1 (0.02)
LDH increased	1 (0.02)
Hyperglycemia	1 (0.02)
Sugar blood level increased	1 (0.02)
Hypercholesterolemia	1 (0.02)
Cholesterol serum elevated	3 (0.07)
Cholesterol total elevated	2 (0.04)
Hyperuricemia	2 (0.04)
Uric acid blood increased	1 (0.02)
Hypoglycemia	1 (0.02)
Sugar in the urine	1 (0.02)
Chloride serum increased	1 (0.02)
Triglyceride increased	2 (0.04)
HDL cholesterol decreased	1 (0.02)
General cardiovascular disorders	27 (0.59)
Hypotension postural	1 (0.02)
Cardiac failure	3 (0.07)
Hypotension	15 (0.33)
Blood pressure dropped	1 (0.02)
Blood pressure decreased	3 (0.07)
Cardiothoracic ratio increased	5 (0.11)
Heart rate and rhythm disorders	34 (0.74)
Extrasystole ventricular	1 (0.02)
Bradycardia	24 (0.52)
Sinus bradycardia	2 (0.04)
Bradycardiac tendency	1 (0.02)
Heart pounding	4 (0.09)
Fibrillation atrial	1 (0.02)
Tachycardia	1 (0.02)
Sinus tachycardia	1 (0.02)
Vascular (extracardiac) disorders	3 (0.07)

Continued next page

Table II. Contd

System Organ Class and preferred term	Number of ADRs (incidence rate [%])
Pulmonary infarction	1 (0.02)
Coldness of lower extremities	1 (0.02)
Coldness of limbs	1 (0.02)
Respiratory system disorders	18 (0.39)
Asthma bronchial	2 (0.04)
Status asthmaticus	1 (0.02)
Breath shortness	2 (0.04)
Respiratory distress	2 (0.04)
Breathing difficult	1 (0.02)
Respiration stimulated	1 (0.02)
Coughing	3 (0.07)
Cough	1 (0.02)
Stridor	3 (0.07)
Nasal obstruction	2 (0.04)
Red blood cell disorders	1 (0.02)
Anemia	1 (0.02)
Urinary system disorders	7 (0.15)
Creatinine blood increased	2 (0.04)
Albuminuria	1 (0.02)
Urinary incontinence	1 (0.02)
BUN increased	2 (0.04)
Nocturia	1 (0.02)
Urinary frequency	1 (0.02)
Reproductive disorders, male	1 (0.02)
Erection decreased	1 (0.02)
Body as a whole, general disorders	28 (0.61)
Face edema	2 (0.04)
Chest pain	1 (0.02)
Chest discomfort	1 (0.02)
Chest distress	1 (0.02)
Edema generalized	1 (0.02)
Cold sweat	1 (0.02)
Fatigueability	2 (0.04)
Fatigue	3 (0.07)
Malaise	5 (0.11)
Feeling bad	2 (0.04)
Fatigueability generalized	1 (0.02)
Feeling unwell	1 (0.02)
Edema	1 (0.02)
Hot flushes facial	1 (0.02)
Feeling of hot flushes	1 (0.02)
Edema of lower extremities	1 (0.02)
Edema of extremities	1 (0.02)

Continued

Table II. Contd

System Organ Class and preferred term	Number of ADRs (incidence rate [%])
Edema palmar	1 (0.02)
Lower extremities, weakness of	1 (0.02)
Weakness	5 (0.11)
Cardiac failure aggravated	1 (0.02)

a Number of participating medical institutions (n = 552); number of participating patients (n = 4574); number of patients with ADRs (n = 197); number of ADRs (n = 265); overall incidence of ADRs = 4.31%.

ALP = alkaline phosphatase; **BUN** = blood urea nitrogen; **GOT** = glutamic oxaloacetic transaminase; **GPT** = glutamic pyruvic transaminase; **HDL** = high-density lipoprotein; **LDH** = lactate dehydrogenase.

Mean changes from baseline were small for all the laboratory parameters, including glucose and lipid metabolic-related parameters, without inducing clinically relevant problems.

Efficacy

Changes in Blood Pressure and Pulse Rate

Figure 2 shows changes in BP and pulse rate from baseline to week 12 for those patients among the efficacy population of 4422 for whom these measurements were taken. BP and pulse rate were significantly reduced from baseline at week 2 and continued to gradually reduce until week 12 ($p < 0.001$ for both).

Changes in BP and pulse rate from baseline are summarized in table V for patients who (i) had these measurements taken before and after the initiation of carvedilol treatment (all patients); (ii) had not previously used antihypertensive medications at the time of initiation of carvedilol treatment (carvedilol alone); and (iii) had previously used antihypertensive medications (concomitant use of CCBs, concomitant use of ACEIs, concomitant use of diuretics, concomitant use of α -blockers) at initiation of carvedilol treatment.

Respective mean SBP and DBP for the total efficacy population were 168.2 ± 18.6 mmHg and 95.7 ± 11.3 mmHg at baseline; these were reduced to 144.3 ± 17.3 mmHg and 83.4 ± 10.8 mmHg at week 12. Mean change value from baseline to week 12 (the value at week 12 subtracted by the baseline value) was -23.9 ± 20.3 mmHg for SBP and -12.3 ± 12.4 mmHg for DBP, indicating a significant reduction ($p < 0.001$ for both). Mean

Table III. Adverse drug reactions (ADRs) by selected demographic factors of patients in the safety population

Demographic factor/stratum	No. of patients	No. of patients with ADRs (%)	p-Value ^a
TOTAL	4574	197 (4.31)	
Sex			
Male	2203	90 (4.09)	0.512
Female	2369	107 (4.52)	
Unknown/not stated	2	0 (0.00)	
Age (years)			
<15	0		0.025
15 to <65	2816	106 (3.76)	
≥65	1757	91 (5.18)	
Unknown/not stated	1	0 (0.00)	
In-/outpatient status			
Inpatient	173	10 (5.78)	0.069
Outpatient	4177	174 (4.17)	
In- ↔ outpatient	173	13 (7.51)	
Unknown/not stated	51	0 (0.00)	
Severity (WHO classification)			
Grade I	2713	104 (3.83)	<0.001
Grade II	1037	41 (3.95)	
Grade III	586	45 (7.68)	
Unknown/not stated	238	7 (2.94)	
Complications			
No	1876	54 (2.88)	<0.001
Yes	2591	137 (5.29)	
Unknown/not stated	107	6 (5.61)	
Hepatic disease			
no	4003	168 (4.20)	0.213
yes	536	29 (5.41)	
unknown/not stated	35	0 (0.00)	
Renal disease			
no	4244	174 (4.10)	0.010
yes	289	22 (7.61)	
unknown/not stated	41	1 (2.44)	
Heart disease			
no	3678	150 (4.08)	0.093
yes	853	46 (5.39)	
unknown/not stated	43	1 (2.33)	
Diabetes mellitus			
no	4034	172 (4.26)	0.417
yes	500	25 (5.00)	
unknown/not stated	40	0 (0.00)	
Previous antihypertensive medication			
No	1822	56 (3.07)	<0.001

*Continued***Table III.** Contd

Demographic factor/stratum	No. of patients	No. of patients with ADRs (%)	p-Value ^a
Yes	2471	133 (5.38)	
Unknown/not stated	281	8 (2.85)	
Initial carvedilol daily dose (mg)			
<10	7	0 (0.00)	0.496
10	2039	97 (4.76)	
20	2509	99 (3.95)	
≥21	18	1 (5.56)	
Unknown/not stated	1	0 (0.00)	
Duration of carvedilol treatment (mo)			
<1	254	83 (32.68)	<0.001
≥1	4316	114 (2.64)	
Unknown/not stated	4	0 (0.00)	
Concomitant medications			
No	1124	37 (3.29)	0.051
Yes	3322	156 (4.70)	
Unknown/not stated	128	4 (3.13)	
Other antihypertensive medications			
no	2280	84 (3.68)	0.041
yes	2293	113 (4.93)	
unknown/ not stated	1	0 (0.00)	

a Analysis using the Fisher's direct probability method was performed, except for 'unknown/not stated' categories.

In- ↔ outpatient = patients who were constantly in and out of hospital.

pulse rate in all patients was 76.2 ± 12.6 beats per minute (beats/min) at baseline and 69.7 ± 8.8 beats/min at week 12. The mean change value was -6.6 ± 11.2 beats/min, indicating a significant decrease from baseline to week 12 ($p < 0.001$). Respective mean change values from baseline to week 12 for SBP and DBP were -22.7 ± 18.8 mmHg and -12.2 ± 12.2 mmHg in patients treated with carvedilol alone; -26.1 ± 22.4 mmHg and -12.7 ± 13.1 mmHg in patients who received concomitant CCBs; -25.4 ± 23.3 mmHg and -11.9 ± 13.0 mmHg in those who received ACEIs; -26.3 ± 22.0 mmHg and -13.0 ± 13.3 mmHg in the patients who received diuretics; and -24.4 ± 21.0 mmHg and -11.5 ± 11.1 mmHg in patients who received α -blockers, demonstrating a significant difference in SBP/DBP between baseline and week 12 in all strata ($p < 0.001$ for all). No significant difference in the change value for SBP or DBP was seen for the cohort that had previously used anti-

hypertensive drugs ($p=0.836$ for SBP; $p=0.515$ for DBP). Therefore, carvedilol had similar clinical efficacy when used alone or in combination with other antihypertensive medications.

Assessment of Efficacy

The results of the physicians' assessment of efficacy (based on an antihypertensive effect of carvedilol) are presented in table VI. Among the 4422 patients in the efficacy population, 58.1% (2571 of 4422 patients) were judged as 'decreased' and 84.8% (3748 of 4422 patients) as 'decreased' or 'tended to be decreased'.

Achievement Rate of Target Blood Pressure

Figure 3 illustrates achievement of target BP at week 12. For the target BP of 140/90 mmHg, the

achievement rate at week 12 after the initiation of carvedilol was 31.3% for all patients, 29.5% for those treated with carvedilol alone, 34.8% for those with concomitant CCBs, 31.3% with ACEIs, 31.8% with diuretics, and 32.4% for those with α -blockers. For comparison, the achievement rate in the efficacy population before the initiation of carvedilol had been 3.0%. There was no significant difference in the achievement rate between the antihypertensive medications previously used ($p=0.475$). For the intermediate target BP (150/90 mmHg) at the start of the survey, the achievement rate at week 12 was 53.0% for all patients, 52.2% for those with carvedilol alone, 55.9% for those with CCBs, 46.3% for those with ACEIs, 55.8% for those with diuretics, and 44.1% for those with α -blockers.

Table IV. Mean changes in laboratory test parameters in the safety population

Parameter	No. of pts	Baseline		Week 12	
		mean	SD	mean	SD
Red blood cell count ($\times 10^4/\text{mm}^3$)	1434	442.5	57.5	436.6	55.3
White blood cell count ($/\text{mm}^3$)	1433	6,119	1942	5880	1659
Hemoglobin (g/dL)	1427	13.6	1.9	13.7	4.9
Hematocrit (%)	1418	41.0	5.2	40.8	10.0
Platelet count ($\times 10^4/\text{mm}^3$)	1315	23.3	14.6	22.8	14.8
Total protein (g/dL)	1285	7.21	0.60	7.18	1.97
Albumin (g/dL)	703	4.97	6.06	4.86	5.94
Total cholesterol (mg/dL)	1496	203.6	38.4	197.7	34.6
Triglyceride (mg/dL)	1326	155.1	100.1	147.1	80.2
LDL (mg/dL)	158	187.3	144.1	179.4	137.6
HDL (mg/dL)	855	52.2	21.4	50.7	22.0
BUN (mg/dL)	1416	17.6	10.9	18.0	12.1
Creatinine (mg/dL)	1352	1.15	1.54	1.18	1.71
Uric acid (mg/dL)	1210	5.45	2.05	5.51	2.36
Na (mEq/L)	1194	141.3	2.9	141.4	2.7
Ca (mEq/L)	414	8.23	6.92	8.21	6.92
K (mEq/L)	1194	4.57	5.90	4.65	6.61
Cl (mEq/L)	1135	103.3	3.8	103.5	4.0
AST (GOT) [U]	1524	27.0	20.3	25.0	17.8
ALT (GPT) [U]	1532	25.5	27.1	23.2	20.7
Al-P (IU)	399	180.0	80.1	176.7	74.1
LDH (U)	1095	355.6	93.9	345.0	84.6
CPK (IU/L)	538	96.4	65.3	89.1	46.4
Fasting blood glucose (mg/dL)	892	112.8	44.5	108.6	36.4

Al-P= alkaline phosphatase; **ALT (GOT)**= alanine aminotransferase (glutamic oxaloacetic transaminase); **AST (GPT)**= aspartate aminotransferase (glutamic pyruvic transaminase); **BUN**= blood urea nitrogen; **CPK**= creatine phosphokinase; **HDL**= high-density lipoprotein; **LDH**= lactate dehydrogenase; **LDL**= low-density lipoprotein; **pts**= patients.

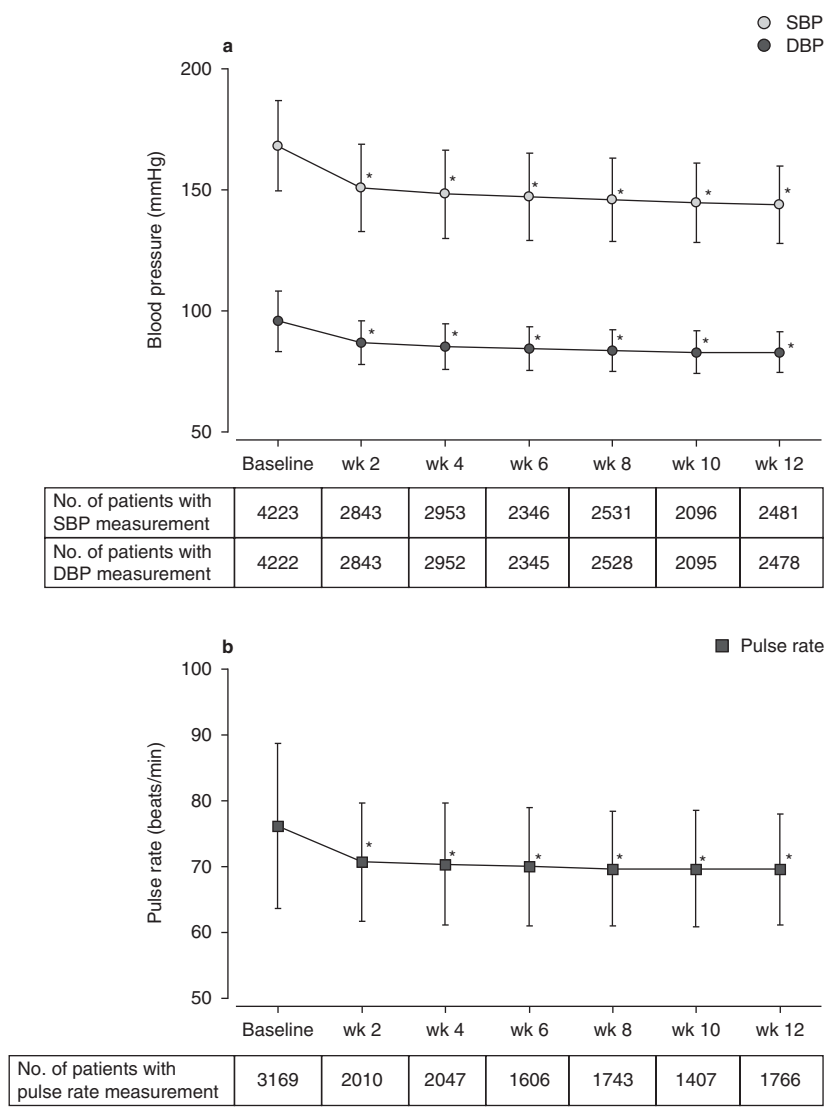


Fig. 2. Changes (mean±SD) in (a) blood pressure and (b) pulse rate in the efficacy population. **DBP**=diastolic blood pressure; **SBP**=systolic blood pressure. * $p<0.001$ (Dunnett's multiple comparison).

Review of Elderly Patients, those with Diabetes Mellitus or Renal Disease

Changes in Blood Pressure and Pulse Rate

Table VII shows changes in BP and pulse rate from baseline to week 12 in elderly patients (aged ≥65 years), and those with diabetes complications

or renal disease complications among the efficacy population. The respective values of SBP and DBP were reduced from 171.5 ± 19.1 mmHg and 92.1 ± 11.4 mmHg at baseline to 145.5 ± 18.5 mmHg and 80.2 ± 10.7 mmHg at week 12 in the elderly group; from 171.0 ± 18.7 mmHg and 93.7 ± 12.4 mmHg at baseline to 147.4 ± 20.0 mmHg and

82.8 ± 11.1 mmHg at week 12 in those with diabetes complications; and from 173.7 ± 22.5 mmHg and 93.9 ± 13.0 mmHg at baseline to 146.5 ± 20.0 mmHg and 82.6 ± 11.3 mmHg at week 12 in those with renal disease complications. There was a significant reduction in all the subgroups ($p < 0.001$ for all).

Changes in Fasting Blood Glucose in Patients with Diabetes and in Creatinine in Those with Renal Disease

Figure 4 illustrates changes from baseline to week 12 in fasting blood glucose in patients with diabetes complications and in creatinine levels in those with renal disease complications in the 4574 patients in the safety population. The fasting blood glucose level in patients with diabetes

complications was 163.4 ± 64.7 mg/dL at baseline and this was reduced to 148.5 ± 54.1 mg/dL at week 12. The creatinine level in those with renal disease complications was 3.28 ± 3.83 mg/dL at baseline, which was changed to 3.54 ± 4.24 mg/dL at week 12.

Discussion

The mechanism of antihypertensive action of β -blockers has not been established. The possible main mechanisms may be linked to a decrease in cardiac output, a reduction in the production/release of renin in the kidney, and a reduction in the release of sympathomimetic substances from the CNS. A reduction in the release of sympathomimetic

Table V. Changes in blood pressure and pulse rate for each concomitant medication in the efficacy population

Parameter (mean ± SD)	No. of pts	Baseline	Week 12	Δ	p-Value
All patients					
SBP (mmHg)	4089	168.2 ± 18.6	144.3 ± 17.3	-23.9 ± 20.3	<0.001
DBP (mmHg)	4088	95.7 ± 11.3	83.4 ± 10.8	-12.3 ± 12.4	<0.001
Pulse rate (beats/min)	2796	76.2 ± 12.6	69.7 ± 8.8	-6.6 ± 11.2	<0.001
Carvedilol alone					
SBP (mmHg)	2164	167.3 ± 17.4	144.6 ± 16.3	-22.7 ± 18.8	<0.001
DBP (mmHg)	2163	96.2 ± 10.7	84.0 ± 10.5	-12.2 ± 12.2	<0.001
Pulse rate (beats/min)	1514	76.0 ± 12.6	69.3 ± 8.8	-6.8 ± 11.3	<0.001
Concomitant use of CCBs^a					
SBP (mmHg)	1334	168.9 ± 20.2	142.8 ± 18.6	-26.1 ± 22.4	<0.001
DBP (mmHg)	1334	94.9 ± 12.1	82.2 ± 11.1	-12.7 ± 13.1	<0.001
Pulse rate (beats/min)	894	76.8 ± 12.8	70.4 ± 9.1	-6.4 ± 11.3	<0.001
Concomitant use of ACEIs^a					
SBP (mmHg)	600	172.0 ± 20.3	146.6 ± 20.2	-25.4 ± 23.3	<0.001
DBP (mmHg)	600	95.9 ± 12.3	84.0 ± 12.2	-11.9 ± 13.0	<0.001
Pulse rate (beats/min)	457	76.4 ± 13.1	70.3 ± 9.2	-6.2 ± 11.7	<0.001
Concomitant use of diuretics^a					
SBP (mmHg)	154	172.3 ± 22.8	146.0 ± 19.8	-26.3 ± 22.0	<0.001
DBP (mmHg)	154	94.7 ± 13.0	81.6 ± 10.8	-13.0 ± 13.3	<0.001
Pulse rate (beats/min)	118	75.5 ± 13.9	69.7 ± 9.4	-5.8 ± 12.0	<0.001
Concomitant use of α-blockers^a					
SBP (mmHg)	102	171.1 ± 19.1	146.7 ± 19.8	-24.4 ± 21.0	<0.001
DBP (mmHg)	102	95.6 ± 10.5	84.0 ± 11.3	-11.5 ± 11.1	<0.001
Pulse rate (beats/min)	71	77.2 ± 14.7	69.6 ± 8.7	-7.5 ± 12.5	<0.001

a Concomitant antihypertensive medications used at the initiation of carvedilol treatment; if patients used two or more concomitant medications, they were counted for each medication.

ACEIs=angiotensin-converting enzyme inhibitors; **CCBs**=calcium channel blockers; **DBP**=diastolic blood pressure; **pts**=patients; **SBP**=systolic blood pressure; Δ indicates change.

Table VI. Assessment of efficacy by the physicians (based on an antihypertensive effect of carvedilol) in the efficacy population

Physician's assessment	No. of patients	Percentage (95% CI)
Decreased	2571	58.1 (56.7, 59.6)
Tended to decrease	1177	
Decreased and tended to decrease	3748	84.8 (83.7, 85.8)
Unchanged	582	
Increased	92	

substances by β -blockers has been demonstrated to play a role in the primary and secondary prevention of cardiovascular events through several mechanisms,^[23,24] especially for hypertension complicated with ischemic heart disease. In Japan, over 20 types of β -blockers have been used in clinical practice. It has been suggested that β -blockers could have different effects on the long-term prognosis of hypertensive patients depending on their lipophilicity (water solubility), intrinsic sympathomimetic action, membrane-stabilizing action, vasodilation, and any additional actions (e.g. antioxidant), as well as their selectivity at β_1 receptors. Hence, it is reasonable to suggest that it would be difficult to categorize these drugs into

one group, despite the fact that they are classified as one drug class (i.e. β -blockers). In addition, since β -blockers are contraindicated in some patient groups and are not recommended for elderly patients or those with diabetes, it may be possible that potential target patient populations are excluded from receiving this treatment.

Carvedilol is a nonselective β -blocking cardiac agent. In addition to its potent antioxidant action, it was developed to have an additional α_1 antagonist action (a blocking ratio of $\alpha : \beta = 1 : 8$) to reduce some of the risks associated with other β -blockers such as increased peripheral vascular resistance, excessively impaired cardiac functions, and adverse effects on glucose/lipid metabolism.^[25-28] As expected, in large-scale international clinical studies, the clinical efficacy of carvedilol was demonstrated to be different from that of conventional β -blockers.^[14,19] An observational drug use survey in a large number of patients would be of certain significance to interpret whether data from such large-scale clinical studies are applicable in daily medical practice. Therefore, we conducted a prospective surveillance study on the use of carvedilol to confirm its safety and efficacy and gather information about its actual use in

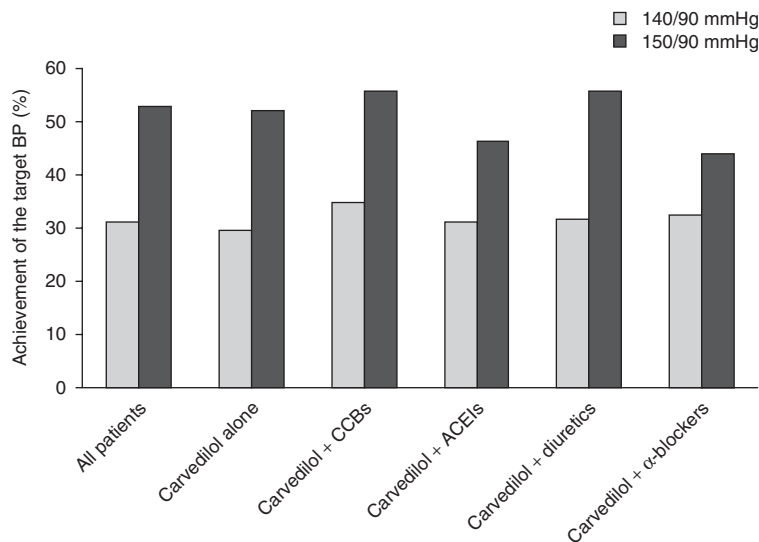


Fig. 3. Achievement of target blood pressure (BP) at week 12 in the efficacy population. **ACEIs**=Angiotensin-converting enzyme inhibitors; **CCBs**=calcium channel blockers.

Table VII. Changes in blood pressure and pulse rate in elderly patients, those complicated with diabetes mellitus, and those with renal disease in the efficacy population

Parameter (mean \pm SD)	No. of pts	Baseline	Week 12	Δ	p-Value
Elderly patients (≥ 65 y)					
SBP (mmHg)	1594	171.5 \pm 19.1	145.5 \pm 18.5	-26.0 \pm 21.7	<0.001
DBP (mmHg)	1593	92.1 \pm 11.4	80.2 \pm 10.7	-11.9 \pm 12.3	<0.001
Pulse rate (beats/min)	1071	75.8 \pm 12.5	69.2 \pm 9.1	-6.5 \pm 11.2	<0.001
Patients with diabetes					
SBP (mmHg)	446	171.0 \pm 18.7	147.4 \pm 20.0	-23.6 \pm 21.0	<0.001
DBP (mmHg)	446	93.7 \pm 12.4	82.8 \pm 11.1	-10.9 \pm 12.3	<0.001
Pulse rate (beats/min)	321	76.7 \pm 13.8	70.4 \pm 9.8	-6.3 \pm 12.1	<0.001
Patients with renal disease					
SBP (mmHg)	258	173.7 \pm 22.5	146.5 \pm 20.0	-27.2 \pm 23.6	<0.001
DBP (mmHg)	258	93.9 \pm 13.0	82.6 \pm 11.3	-11.3 \pm 12.1	<0.001
Pulse rate (beats/min)	199	77.6 \pm 12.4	70.4 \pm 8.9	-7.1 \pm 12.8	<0.001

DBP = diastolic blood pressure; pts = patients; SBP = systolic blood pressure; Δ indicates change.

Japanese hypertensive patients in daily clinical practice.

We collected data on 4961 patients from 561 medical institutions nationwide; 4574 patients were evaluable for safety and 4422 were for efficacy. The overall incidence rate of ADRs was 4.31% in the survey. The most commonly reported ADRs were 24 events of bradycardia, 19 events of dizziness, 15 events of hypotension, and nine events each of headache and light-headed feeling; all could be linked to the pharmacologic action of carvedilol. The incidence and types of ADRs reported in our survey were similar to those observed in clinical studies conducted prior to approval.

A review of ADRs stratified by selected demographic factors showed a significant difference in the incidence rate of ADRs between strata for age, severity (WHO classification), presence/absence of complications (renal disease), previous use of antihypertensive medications before initiation of carvedilol, total number of days of carvedilol treatment, and concomitant use of other antihypertensive medications.

According to stratification by age, the incidence of ADRs was higher in elderly patients (aged ≥ 65 years) in whom there was a significantly higher incidence of general cardiovascular disorders ($p < 0.001$). Organ function generally tends to decline with age, therefore, in elderly patients, carvedilol should be initiated at lower doses be-

cause the drug is likely to excessively exhibit its pharmacologic actions when hepatic metabolic capacity is decreased, and because an excessive or rapid decrease in BP can cause ischemic events in important organs such as the heart, kidney, and brain.

A significantly higher incidence of ADRs was seen in the stratum of grade III as stratified by severity (WHO classification) and in that of patients with renal disease complications as stratified by presence/absence of complications (renal disease). Both strata had similar patterns of ADRs, as evidenced by the fact that the incidence rate of whole-body general disorders; general cardiovascular disorders; central and peripheral nervous system disorders; and respiratory system disorders were higher in both strata. The subgroup of patients with renal disease complications included a relatively high proportion of patients with WHO grade III. This could explain the higher incidence of ADRs in patients with WHO grade III; that is, the higher incidence rate in this subgroup could be affected by complications of renal disease. Carvedilol is metabolized in the liver and excreted in feces, but does not seem to be significantly affected by renal function. In patients with severe renal impairment, however, blood drug concentrations are likely to be increased.^[29] Hence, carvedilol should be administered with caution to patients with renal disease. In patients with renal

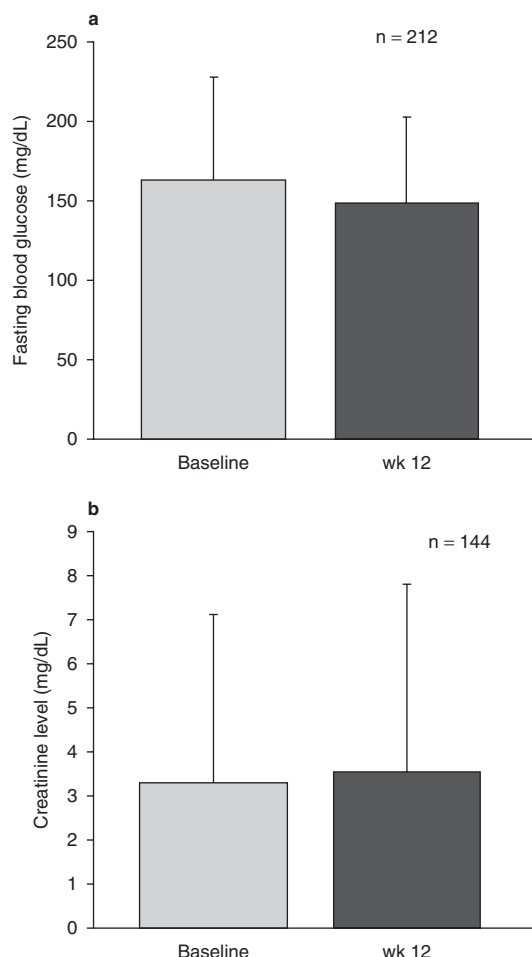


Fig. 4. Changes (mean \pm SD) between baseline and week 12 in the safety population in (a) fasting blood glucose in patients complicated with diabetes mellitus and (b) in creatinine levels in those complicated with renal disease.

disease complications, no ADRs related to renal function (urinary system disorders), such as decreased renal function or albuminuria, were reported during the survey.

Stratification by previous use of antihypertensive medications showed a higher incidence of ADRs in patients with previous use. These patients could be characterized by having a long duration of the disease and multiple organ dysfunction due to their complications. When analyzed by disease duration, the incidence of ADRs tended to be increased with longer duration. Therefore, it would

be likely that the higher incidence rate in patients with previous use would be due to the longer duration of the disease.

When analyzed by the total number of days of carvedilol treatment, patients who had received carvedilol for <1 month were found to have a higher incidence rate of ADRs. This may be because they tended to have ADRs during the early period of treatment and discontinued the drug at that time.

When analyzed by concomitant use of other antihypertensive medications, patients who had concomitantly used other antihypertensive medications had a higher incidence of ADRs; the incidence of general cardiovascular disorders was significantly higher ($p=0.019$). Among patients who concomitantly used other antihypertensive medications, those who used CCBs accounted for the majority (74.1% [1698 of 2293 patients]). It would be likely that concomitant use of carvedilol with CCBs, especially with CCBs, which have an inhibitory effect on cardiac conduction and can decrease cardiac contractility and heart rate, would enhance each others actions. Carvedilol is cautioned for use with CCBs as indicated in the “Drug Interactions (Precautions for Coadministration)” section in the current package insert (Daiichi Sankyo Co., Ltd., Tokyo, Japan, 2007).

In the efficacy population, mean baseline SBP and DBP values, which were 168.2 ± 18.6 mmHg and 95.7 ± 11.3 mmHg, respectively, were significantly decreased to 144.3 ± 17.3 mmHg and 83.4 ± 10.8 mmHg at week 12. BP was significantly reduced at week 2 and was gradually reduced thereafter until week 12. In patients who received carvedilol alone who had not received any other antihypertensive drugs, respective mean change values for SBP and DBP from baseline to 12 weeks after treatment were -22.7 mmHg and -12.2 mmHg, while for the cohorts that had previously used antihypertensive drugs at initiation of carvedilol treatment, respective mean change values for SBP and DBP ranged from -24.4 to -26.3 mmHg and from -11.5 to -13.0 mmHg; there was no significant difference between patients that received carvedilol alone and those that previously and concomitantly used other antihypertensive agents. Hence, carvedilol was found to exhibit a

stable antihypertensive effect when used alone and in combination with other antihypertensive drugs. For the target BP goal (140/90 mmHg) specified in JSH 2004,^[1] the achievement rate ranged from 31.3% to 34.8% in the subgroups classified as previous users of antihypertensive agents, and there was no significant difference between the antihypertensive medications previously used. Therefore, carvedilol in any of the combinations achieved the target BP goal in a similar manner, suggesting that the efficacy of this drug is favorable in combination with any other antihypertensive drug. Carvedilol could also be described as being very useful with proven clinical efficacy not only when used as a first-choice treatment for patients who have not received any previous antihypertensive drugs, but also when used as an additional treatment for those who have been receiving another antihypertensive drug. However, this survey was completed before ARBs, which are widely-used antihypertensive drugs, were launched in Japan; hence, further surveys are necessary to investigate the combined effect of carvedilol and ARBs.

In this survey, 31.3% of all patients achieved the BP goal (140/90 mmHg) specified in the JSH 2004.^[1] This achievement rate differed from the proportion (58.1%) of patients judged as decreased by their physicians. In contrast, 53.0% of all patients had achieved the tentative goal (150/90 mmHg) around the time of starting the survey; this rate was similar to the proportion of patients who were judged decreased. Therefore, it can be presumed that the physicians attending the survey were satisfied with the antihypertensive effect of carvedilol to some extent.

It is known that in elderly patients, reduced activity of the renin-angiotensin system is seen as one of the age-dependent humoral factors related to BP control and that renin activity is generally low. One of the mechanisms of the antihypertensive action of β -blockers is thought to be blockade of β -receptors in the juxtaglomerular cells, which results in a decrease in release of renin from the kidney. It has been reported that the antihypertensive effect of β -blockers can be reduced in hypertensive patients with low renin activity.^[30-33] Therefore, it might be possible that the anti-

hypertensive effect would be reduced in elderly hypertensive patients with low renin activity. In this survey, however, the respective SBP and DBP values in the elderly patients were 171.5 ± 19.1 mmHg and 92.1 ± 11.4 mmHg at baseline, and 145.5 ± 18.5 mmHg and 80.2 ± 10.7 mmHg at the end of treatment; these changes were similar to those seen in the whole study population, which included a high percentage of non-elderly patients (60%). A decrease in the antihypertensive effect of carvedilol was not observed in elderly patients in this survey. Thus, carvedilol was demonstrated to be effective and also of use in elderly hypertensive patients.

In Japanese and overseas guidelines,^[1-4] the importance of good BP control has been emphasized especially for hypertensive patients with diabetes and those with renal disease, and a more strict BP goal has been set for such patients. For those with diabetes, blood glucose, as well as BP, has to be strictly controlled and antihypertensive drugs that have no negative impact on glucose metabolism are recommended. Many β -blockers can negatively affect glucose metabolism and it is generally said that caution should be exercised when these drugs are used by patients with diabetes. In the 2007 Guidelines for the Management of Arterial Hypertension (ESH/ESC 2007),^[4] the combination of β -blockers with thiazide diuretics is not recommended for patients with a high risk of metabolic syndrome or diabetes. Carvedilol, a vasodilating β -blocker, is more likely to have a small negative effect on glucose metabolism and decrease the initial onset of diabetes as compared with other β -blockers.^[34] From the results of the GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) trial, Bakris et al.^[14] reported that carvedilol improves insulin sensitivity without any effect on glycated hemoglobin, while controlling BP well. Our survey included 500 patients with diabetes complications in whom the drug was found to have good antihypertensive effect without a significant difference in the incidence rate of ADRs compared with those without diabetes complications. Among reported metabolic and nutritional disorders, the ADRs related to glucose metabolism were only one event each of hyper-

glycemia, sugar blood level increased,¹ hypoglycemia, and sugar in the urine¹ from three patients. All of these ADRs were observed in patients with diabetes complications, but none were considered serious. Fasting blood glucose levels in patients with diabetes were 163.4 ± 64.7 mg/dL at baseline and 148.5 ± 54.1 mg/dL at the end of treatment, without an adverse change from baseline. Among the 500 patients with diabetes complications, 16 started or additionally took antidiabetic medications during the course of carvedilol treatment, and seven received antidiabetic medications at the initiation of carvedilol treatment but discontinued these medications during carvedilol treatment. Even considering the addition or discontinuation of antidiabetic medications in these 23 patients, carvedilol is not believed to have a negative impact on glucose metabolism. Hence, in this survey, as reported previously, the safety of carvedilol was demonstrated with no adverse effects on glucose metabolism, even in patients with diabetes complications.

For patients with renal disease complications, as for patients with diabetes complications, strict BP control is necessary and first-choice drugs are ACEIs, which have a renal-protective effect, and renin-angiotensin system inhibitors, such as ARBs. If the BP goal is not achieved with these drugs, multidrug therapy will be needed. In this case, β -blockers would be a second or third choice when used in combination, in order to maintain good BP control. In this survey, the respective SBP and DBP values in the patients with renal disease complications were 173.7 ± 22.5 mmHg and 93.9 ± 13.0 mmHg at baseline and were decreased to 146.5 ± 20.0 mmHg and 82.6 ± 11.3 mmHg at week 12, suggesting a good antihypertensive effect of carvedilol, even in this patient subgroup. The creatinine level in patients with renal disease was 3.28 ± 3.83 mg/dL at baseline and 3.54 ± 4.24 mg/dL at the end of treatment. As indicated by the level at baseline, this subgroup of patients had severe renal dysfunction and was being treated in daily clinical practice; thus, the change in creatinine levels seen in

this subgroup is not thought to be clinically relevant. Therefore, carvedilol also demonstrated to have a favorable antihypertensive effect in patients with renal disease complications, while not aggravating their renal function.

In conclusion, carvedilol was confirmed to be safe and effective when used in patients with hypertension in daily clinical practice, and was also safely used with a good antihypertensive effect in elderly patients and in those with diabetes or renal disease complications.

Conclusions

We conducted a drug use survey of Artist[®] tablets (carvedilol) in Japanese patients with hypertension during a period from October 1993 to September 1996. We collected data on 4961 patients from 561 medical institutions nationwide. The drug was investigated for safety in 4574 patients and for efficacy in 4422 patients. The results are summarized in the following five points:

1. The overall incidence rate of ADRs was 4.31% (197 of 4574 patients). The most common ADR was bradycardia, for which 24 events were reported, followed by 19 events of dizziness, 15 events of hypotension, and nine events each of headache and light-headed feeling. These ADRs were linked to the pharmacologic action of the drug. The kinds and patterns of ADRs reported in the survey were similar to those observed in clinical trials that had been performed until the time of approval.

2. As stratified by the selected demographic factors, a significantly higher incidence of ADRs was observed in the following strata: elderly patients (aged ≥ 65 years), patients with grade III (WHO classification) hypertension, patients with renal disease complications, patients who previously used antihypertensive medications, and patients who concomitantly used other antihypertensive medications.

3. The respective SBP and DBP values were 168.2 ± 18.6 mmHg and 95.7 ± 11.3 mmHg at baseline. These values were significantly reduced at

1 Observed in the same patient.

week 2 and were gradually reduced thereafter to 144.3 ± 17.3 mmHg and 83.4 ± 10.8 mmHg, respectively, at week 12.

4. The change value for BP from before to after treatment in patients who received carvedilol alone and in those who had previously used antihypertensive drugs ranged from -22.7 mmHg to -26.3 mmHg for SBP and from -11.5 mmHg to -13.0 mmHg for DBP. In these subgroups, achievement of BP goal ($< 140/90$ mmHg) ranged from 29.5% to 34.8%. There was no significant difference in BP goal achievement rates (31.3–34.8%) between the concomitantly used antihypertensive drugs.

5. The change values for SBP and DBP between before and after treatment were -26.0 mmHg and -11.9 mmHg in elderly patients (aged ≥ 65 years), -23.6 mmHg and -10.9 mmHg in those with diabetes complications, and -27.2 mmHg and -11.3 mmHg in those with renal disease complications, demonstrating a good antihypertensive effect of carvedilol in these populations. Carvedilol did not adversely affect glucose metabolism in patients with diabetes complications, or renal function in those with renal disease complications.

The results of this prospective surveillance study on the use of carvedilol in patients with hypertension closely reflect data that have been collected for the approval of the drug. It can be concluded that carvedilol can be safely and effectively used for the treatment of hypertension.

Acknowledgments

The authors would like to thank the physicians for their support for the drug use survey of Artist[®] tablets and for providing valuable data. We also thank Nila Bhana, MSc, of *inScience* Communications, a Wolters Kluwer business, who provided medical writing support funded by Daiichi Sankyo Co., Ltd., Tokyo, Japan.

This study was supported for funding, data collection, and statistical analysis by Daiichi Sankyo Co., Ltd., Tokyo, Japan. Daiichi Sankyo Co., Ltd. was involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the article. In particular, Yasuhiro Nishikawa, MD, provided intellectual advice for the study concept, scientific interpretation of the results, and approval of the article. The authors have no conflicts of interest to declare.

Yasuhiro Nishikawa is currently employed by Global Project Management Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan; Tomoko Iizuka is currently employed by

Pharmacovigilance Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan; and Masahiro Komiya is currently employed by Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan.

This study was originally published in Japanese in the *Journal of Clinical Therapeutics & Medicines* [2007; 23 (12): 1051-72]. The study has been reproduced here in English with kind permission of the publisher, Rinsho Iyaku Inc.

References

1. The Japanese Society of Hypertension & Guidelines Subcommittee of Japanese Society of Hypertension. 2004 guidelines for the management of hypertension [in Japanese]. Life Science Publishing Co., Ltd., Tokyo, Japan, 2004
2. World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; 21: 1983-92
3. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42: 1206-52
4. European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Guidelines Committee. 2007 Guidelines for the management of arterial hypertension. *J Hypertens* 2007; 25: 1105-87
5. Tomlinson B, Bompert F, Graham BR, et al. Vasodilating mechanism and response to physiological pressor stimuli of acute doses of carvedilol compared with labetalol, propranolol and hydralazine. *Drugs* 1988; 36: 37-47
6. Yoshinaga K, Ishii T, Ikeda M, et al. Effect of DQ-2466 (carvedilol) once daily on circadian rhythm of blood pressure in patients with essential hypertension [in Japanese]. *Jpn J Clin Exp Med* 1989; 66: 3684-92
7. Seguchi H, Nakamura H, Aosaki N, et al. Effects of carvedilol on serum lipids in hypertensive and normotensive subjects. *Eur J Clin Pharmacol* 1990; 38 (Suppl. 2): S139-42
8. Goto Y, Tamachi H, Fusegawa Y, et al. Effect of carvedilol on serum lipid in patients with essential hypertension [in Japanese]. *Geriatr Med* 1989; 27: 1691-704
9. Kumahara Y, Ogihara T, Goto Y, et al. Clinical efficacy of carvedilol (DQ-2466) alone in patients with essential hypertension: a multicenter open study [in Japanese]. *Jpn J Clin Exp Med* 1989; 66: 3968-82
10. Yasujima M, Ikeda M, Kumahara Y, et al. Clinical efficacy of a combination of carvedilol (DQ-2466) and thiazide diuretics in patients with essential hypertension: a multicenter open study [in Japanese]. *Jpn J Clin Exp Med* 1990; 67: 658-74
11. Takahata T, Ohta H, Yamamoto Y, et al. Combination therapy of a β -blocker carvedilol (DQ-2466) with a calcium channel blocker nicardipine in patients with essential hypertension [in Japanese]. *Jpn J Clin Exp Med* 1990; 67: 1263-8
12. Takeda T, Kohno M, Ishii T, et al. Clinical efficacy of DQ-2466 (carvedilol) in the treatment of renal parenchymal hypertension: a multicenter open study [in Japanese]. *Jpn J Clin Exp Med* 1990; 67: 312-24
13. Yoshinaga K, Ogihara T, Goto Y, et al. Clinical efficacy of carvedilol (DQ-2466) in patients with essential hyper-

- tension: a double-blind comparative study with nadolol [in Japanese]. *Jpn J Clin Exp Med* 1992; 69: 2593-617
14. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs. metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; 292: 2227-36
 15. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349-55
 16. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001; 357: 1385-90
 17. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344: 1651-8
 18. Hori M, Sasayama S, Kitabatake A, et al. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. *Am Heart J* 2004; 147: 324-30
 19. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; 362: 7-13
 20. Japanese Circulation Society. Guidelines for treatment of chronic heart failure (JCS 2005) [in Japanese]. Omura Printing Co., Ltd.: Yamaguchi, 2005
 21. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. *Circulation* 2005; 112: 154-235
 22. Good Post-Marketing Surveillance Practice [in Japanese; online]. Available from URL: http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe2.cgi?MODE=hourei&DMODE=SEARCH&SMODE=NORMAL&KEYWORD=%90%bb%91%a2%94%cc%94%84%8c%e3%92%b2%8d%b8&EFSNO=597&FILE=FIRST&POS=0&HITSU=83 [Accessed 2011 May 17]
 23. Wikstrand J, Warnold I, Toumilehto J, et al. Metoprolol versus thiazide diuretics in hypertension: morbidity results from the MAPHY study. *Hypertension* 1991; 17: 579-88
 24. Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog cardiovasc Dis* 1985; 27: 335-42
 25. Nakamura K, Kusano K, Nakamura Y, et al. Carvedilol decreases elevated oxidative stress in human failing myocardium. *Circulation* 2002; 105: 2867-71
 26. Tsutamoto T, Wada A, Matsumoto T, et al. Relationship between tumor necrosis factor- α production and oxidative stress in the failing hearts of patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2001; 37: 2086-92
 27. Rossig L, Haendeler J, Mallat Z, et al. Congestive heart failure induces endothelial cell apoptosis: protective role of carvedilol. *J Am Coll Cardiol* 2000; 36: 2081-9
 28. Matsuda Y, Akita H, Terashima M, et al. Carvedilol improves endothelium-dependent dilation in patients with coronary artery disease. *Am Heart J* 2000; 140: 753-9
 29. Interview form of Artist® Tablets. Apr 2007 (ver. 7) [in Japanese]. Daiichi Sankyo Co., Ltd., Tokyo, 2007
 30. Buhler FR, Laragh JH, Baer L, et al. Propranolol inhibition of renin secretion: a specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. *N Engl J Med* 1972; 287: 1209-14
 31. Hollifield JW, Sherman K, Zwagg RV, et al. Proposed mechanisms of propranolol's antihypertensive effect in essential hypertension. *N Engl J Med* 1976; 295: 68-73
 32. Stumpe KO, Kolloch R, Vetter H, et al. Acute and long-term studies of the mechanisms of action of beta-blocking drugs in lowering blood pressure. *Am J Med* 1976; 60: 853-65
 33. Buhler FR, Laragh JH, Sealey JE, et al. Plasma aldosterone-renin interrelationships in various forms of essential hypertension. Studies using a rapid assay of plasma aldosterone. *Am J Cardiol* 1973; 32: 554-61
 34. Torp-Pederson C, Metra M, Charlesworth A, et al. Effect of metoprolol and carvedilol on preexisting and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; 93: 968-73

Correspondence: MS Yoshihiro Mori, Post Marketing Study Management Department, Daiichi Sankyo Co., Ltd., 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan.
E-mail: mori.yoshihiro.kf@daiichisankyo.co.jp